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Original article

Assessment of cardiovascular risk in patients with rheumatoid arthritis using the SCORE risk index

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ABSTRACT

Introduction: Rheumatoid arthritis is an autoimmune disease that causes systemic involvement and is associated with increased risk of cardiovascular disease.
Objective: To analyze the prediction index of 10-year risk of a fatal cardiovascular disease event in female RA patients *versus* controls.
Methods: Case–control study with analysis of 100 female patients matched for age and gender *versus* 100 patients in the control group. For the prediction of 10-year risk of a fatal cardiovascular disease event, the SCORE and modified SCORE (mSCORE) risk indexes were used, as suggested by EULAR, in the subgroup with two or more of the following: duration of disease ≥10 years, RF and/or anti-CCP positivity, and extra-articular manifestations.
Results: The prevalence of analyzed comorbidities was similar in RA patients compared with the control group ($p > 0.05$). The means of the SCORE risk index in RA patients and in the control group were 1.99 (SD: 1.89) and 1.56 (SD: 1.87) ($p = 0.06$), respectively. The means of mSCORE index in RA patients and in the control group were 2.84 (SD = 2.86) and 1.56 (SD = 1.87) ($p = 0.001$), respectively. By using the SCORE risk index, 11% of RA patients were classified as of high risk, and with the use of mSCORE risk index, 36% were at high risk ($p < 0.001$).
Conclusion: The SCORE risk index is similar in both groups, but with the application of the mSCORE index, we recognized that RA patients have a higher 10-year risk of a fatal cardiovascular disease event, and this reinforces the importance of factors inherent to the disease not measured in the SCORE risk index, but considered in mSCORE risk index.

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Avaliação do risco cardiovascular de pacientes com artrite reumatoide utilizando o índice SCORE

Palavras-chave:
Artrite reumatoide
Eventos vasculares
Risco cardiovascular
Fatores de risco

RESUMO

Introdução: Artrite Reumatóide (AR) é uma doença autoimune que determina manifestações sistêmicas e está associada a aumento do risco de evento cardiovascular.
Objetivo: Objetiva-se neste estudo analisar o índice de predição de evento cardiovascular em pacientes do gênero feminino portadores de AR comparados a controles sem a doença.
Métodos: Estudo de caso-controle com análise de 100 pacientes pareadas por gênero e idade *versus* 100 pacientes do grupo controle. Para a predição do risco de evento cardiovascular fatal em 10 anos, utilizamos os índices SCORE e SCORE modificado (mSCORE), conforme sugerido pela EULAR, no subgrupo com 2 ou mais dos seguintes: duração da doença ≥10 anos, positividade para fator reumatoide e/ou anti-CCP, e manifestações extra-articulares.
Resultados: A prevalência das comorbidades analisadas foi similar nas pacientes com AR, em comparação com o grupo controle ($p > 0,05$). As médias do índice SCORE foram 1,99 (DP: 1,89) e 1,56 (DP: 1,87) nas portadoras de AR e nos controles ($p = 0,06$), respectivamente. Com a utilização do índice mSCORE, nas pacientes com AR foi encontrada a média de 2,84 (DP: 2,86) *versus* 1,56 nos controles (DP: 1,87) ($p = 0,001$). Ao utilizar o índice SCORE, 11% dos portadores de AR foram classificados como de alto risco; com o índice mSCORE, 36% obtiveram essa classificação ($p < 0,001$).
Conclusões: O índice SCORE é semelhante nos dois grupos, mas com a aplicação do índice mSCORE, identificamos que os pacientes com AR têm maior risco de evento cardiovascular fatal em 10 anos, com ênfase na importância dos fatores inerentes à doença não mensurados no índice SCORE, mas considerados no índice mSCORE.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown cause characterized mainly by the presence of synovial inflammation, cartilage damage and articular deformity. This disease also determines systemic manifestations and is associated with multiple comorbidities.[1]

Studies have shown that the prevalence of RA is about 0.5–1% of the population,[2,3] and cardiovascular disease is the leading cause of mortality in these patients. In a recently published meta-analysis, the authors found that the risk of mortality from cardiovascular disease (ischemic heart disease and stroke) is 50% higher in RA patients compared to the general population.[4] However, it is clear that early atherosclerosis observed in this group of patients cannot be explained only by traditional cardiovascular risk factors. The formation of atherosclerotic plaques by a chronic inflammatory disease process can come directly (acting on the formation and destabilization of plaque) or indirectly through aortic stiffening, which can lead to left ventricular hypertrophy.[5,6]

In the general population, a number of cardiovascular risk predictive scores has been used, such as the Framingham score and the Systematic Coronary Risk Evaluation index (SCORE), in an attempt to predict risk and acting preventively to avoid unfavorable outcomes. In RA patients, studies on the use of these scores are scarce. According to the recommendations of the European League Against Rheumatism (EULAR), SCORE and modified SCORE (mSCORE) risk indexes should be used for risk prediction in this specific population.

This study aimed to analyze the cardiovascular risk prediction index according to SCORE and mSCORE indexes in RA patients compared to controls without the disease.

Methods

This case–control study was conducted at the Movimento Clinic, a center specialized in rheumatic diseases, at the Reference Polyclinic of UNSUL, and at the Primary Health Care Group (ABS), located in the city of Palhoça (SC).

Medical records of female patients aged between 35 and 70 years old, diagnosed with RA and who met the 1987 disease classification criteria[7] were analyzed. The control subjects were matched for gender and age, and were not healthy people; all members of this group suffered other diseases (except RA), and were referred from an internal medicine clinic, and theoretically were about equally likely exposed to comorbidities and cardiovascular risk factors. The presence of diseases able to increase cardiovascular risk and/or the use of medications which can intervene in assessed variables, were investigated (*e.g.*, antihypertensive, hypoglycemic, hypolipidemic agents). The inclusion of RA patients and of control group subjects followed the criteria for a simple bicaudal random probability sample. Data collection observed a strict standardization for the correct evaluation of the presence of the variables in both groups, and data collection was the responsibility of the same single researcher. The sample size calculation was performed using OpenEpi (Open Source Epidemiologic Statistics for Public Health, Version 2.3.1)

program, with the following parameters: 95% confidence interval (CI 95%); power of 80%; control/case ratio 1:1; rate of exposed controls: 20%; rate of exposed cases: 40%, totaling 100 cases and 100 controls.

Subjects meeting the following criteria[8–10] were considered as comorbidity carriers:

1. High blood pressure (BP): SBP ≥ 140 mm Hg; DBP ≥ 90 mm Hg, or use of antihypertensive medication. Subjects with at least three of these measurements on two different occasions were considered as with hypertension (according to VI Brazilian Guidelines on Hypertension, 2010).
2. Dyslipidemia: LDL cholesterol ≥ 130 mg/dL; Total cholesterol ≥ 200 mg/dL; Triglycerides ≥ 150 mg/dL; HDL ≤ 40 mg/dL; or use of statins (according to the classification of the Third Report of the National Cholesterol Education Program [NCEP] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III] Final Report).
3. Diabetes mellitus (DM): fasting glucose ≥ 126 mg/dL in two samples; glycaemia ≥ 200 mg/dL in a 2-h tolerance test (75 g of glucose); random blood glucose levels ≥ 200 mg/dL; glycated hemoglobin ≥ 6.5% in 2 samples; use of hypoglycemic agents or insulin therapy (according to Standards of Medical Care in Diabetes – 2011).
4. Smoking.

For cardiovascular risk prediction, we used the high-risk SCORE index (Fig. 1) which classifies patients according to age, gender, total cholesterol level, systolic blood pressure (SBP) and tobacco use, using low-and high-risk matrices.[11] Cross-checking of data for each patient provides a cell containing a number representing the numerical value of the SCORE risk index, and a color representing the rate of 10-year risk of a fatal cardiovascular disease event, to which each patient is exposed.

To calculate the mSCORE risk index, the value initially collected from the SCORE risk index was multiplied by a factor of 1.5 for RA patients that met two out of the following three criteria: a disease lasting more than 10 years, RF and/or anti-CCP positivity, and finally, patients with extra-articular manifestations.

Based on calculations of SCORE and mSCORE indexes, patients who were classified with a chance ≥5% of a 10-year

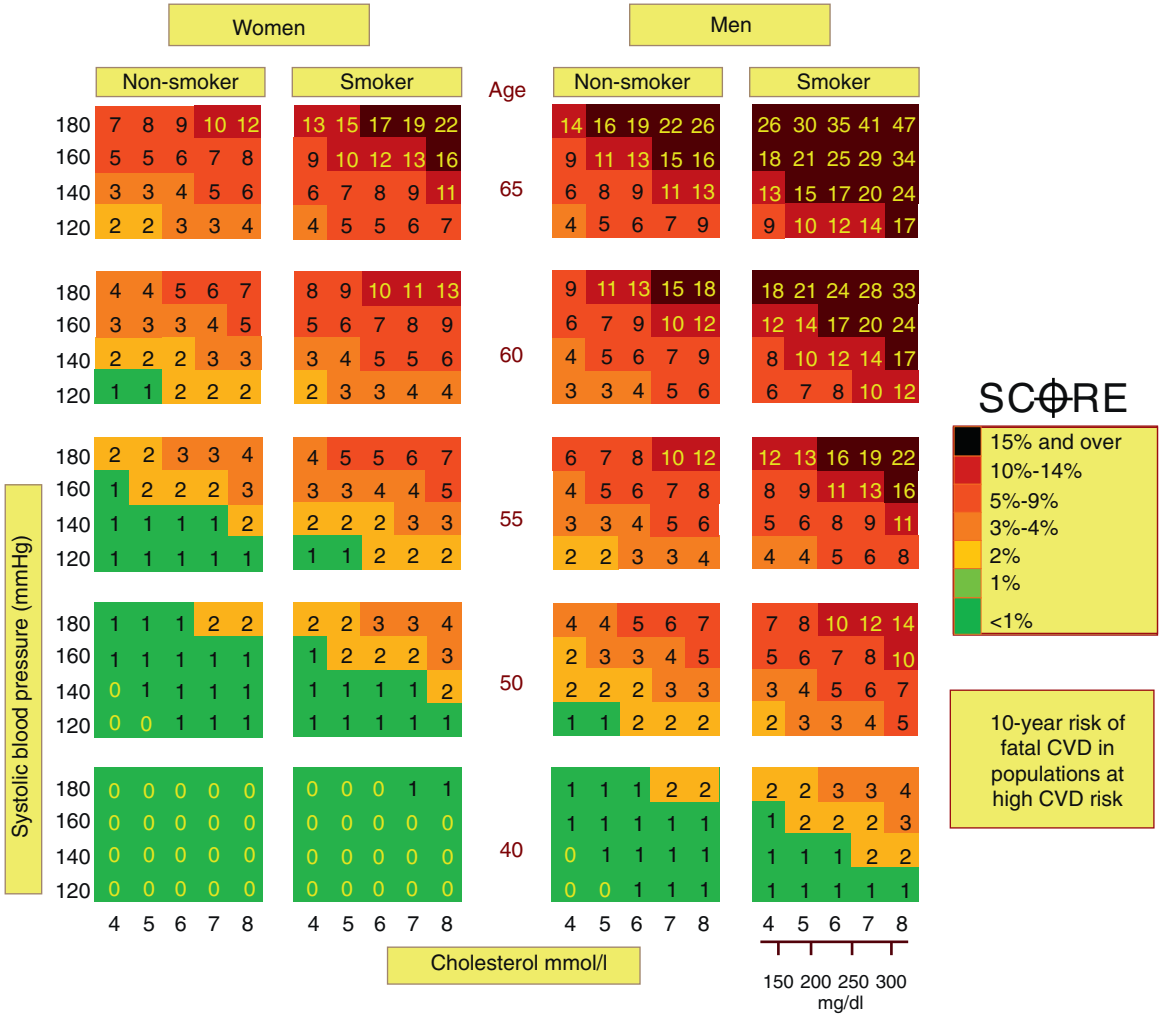

Fig. 1 – SCORE risk index.
***Source*: European Guidelines on CVD Prevention in Clinical Practice (version 2012).**
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Table 1 – Comorbidities in RA patients (cases) and controls.

Variables	Case *n*(%)	Control *n*(%)	Total *n*(%)	*p*-Value	OR (95% CI)
Hypertension				0.32	
Hypertensive	48 (48.0)	55 (55.0)	103 (51.5)		0.75 (0.43–1.31)
Not hypertensive	52 (52.0)	45 (45.0)	97 (48.5)		1
Dyslipidemia				0.29	
Dyslipidemic	69 (69.0)	62 (62.0)	131 (65.5)		1.36 (0.76–2.45)
Not dyslipidemic	31 (31.0)	38 (38.0)	69 (34.5)		1
Diabetes mellitus				0.08	
Diabetic	8 (8.0)	16 (16.0)	24 (12.0)		0.45 (0.18–1.12)
Nondiabetic	92 (92.0)	84 (84.0)	176 (88.0)		1
Heart failure				1	
Yes	2 (2.0)	2 (2.0)	4 (2.0)		1.00 (0.13–7.24)
No	98 (98.0)	98 (98.0)	196 (98.0)		1
Coronary artery disease				0.09	
Yes	5 (5.0)	1 (1.0)	6 (3.0)		5.21 (0.59–45.4)
No	95 (95.0)	99 (99.0)	194 (97.0)		1
Smoking				0.59	
Yes	18 (18.0)	21 (21.0)	39 (19.5)		0.82 (0.41–1.66)
No	82 (82.0)	79 (79.0)	161 (80.5)		1

risk of a fatal cardiovascular disease event were stratified as of "high risk".

The database was developed in Excel and exported to SPSS 16.0 program. Statistical analysis involved the evaluation of normality of quantitative variables. To verify the presence of an association between independent variables and the dependent variable, the Pearson chi-squared test for qualitative variables and the Student's *t* test for quantitative variables were used. OR association measure was used with the respective 95% CIs.

The study was submitted to Research Ethics Committee-UNISUL, having received approval for its realization.

Results

Data of 100 medical records of RA patients were included to compose the case group; and data of 100 medical records of patients without a diagnosis of RA were included to make up the control group. All study participants were female.

The mean age of RA group was 55.4 ± 8.9 years. In the control group, the mean age was 52.3 ± 7 years. The mean duration of disease in RA patients was 14 ± 8 years. Among RA patients, 67% had a diagnosis of RA for more than 10 years. 26% of patients had an extra-articular manifestation (in most cases, pulmonary involvement). Table 1 lists the analysis that determined the association between comorbidities of the study participants. There were no differences in the frequency of comorbidities for both RA and control groups.

Table 2 reports the differences between SCORE and mSCORE risk index means. By analyzing the SCORE risk index for 10-year risk of a fatal cardiovascular disease event for all participants studied, the following means were obtained: 1.99 (SD: 1.89) for RA group and 1.56 (SD: 1.87) for the control group ($p = 0.06$). Using the mSCORE risk index, the following means were obtained: 2.84 (SD = 2.86) in RA group and 1.56 (SD 1.87) in the control group, with statistical significance for this variable ($p = 0.001$).

Table 3 lists the risk stratification associating SCORE and mSCORE indexes. The stratification of patients studied into subgroups with high- and low-risk for a 10-year risk of a fatal cardiovascular disease event was based on the SCORE risk index. This stratification showed that 11% of RA patients and 7% of control group subjects were classified as of high-risk ($p = 0.32$). When using the mSCORE for risk stratification, it was observed that 36% of RA patients and 7% in the control group were classified as of high-risk ($p < 0.001$).

Discussion

In this study, a comparative analysis of patients with and without RA was developed in order to establish SCORE and mSCORE risk indexes for 10-year risk of a fatal cardiovascular disease event in both groups. At first, we identified several comorbidities often present in studied groups and that definitely are related to a worse cardiovascular prognosis.

Table 2 – Means of SCORE and mSCORE risk indexes in cases and controls.

Variables	RA		*p*-Value
	Case Mean (SD)	Control Mean (SD)	
SCORE risk index	1.99 (1.89)	1.56 (1.87)	0.062
mSCORE risk index	2.84 (2.86)	1.56 (1.87)	0.001

RA, rheumatoid arthritis; SCORE, Systematic Coronary Risk Evaluation; mSCORE, modified Systematic Coronary Risk Evaluation.
Source: Elaboration from the author (2012).

Table 3 – Stratification of risk associated to SCORE and mSCORE risk indexes.

Variables	RA		Total	*p*-Value	OR (95% CI)
	Case *n*(%)	Control *n*(%)	*n*(%)		
SCORE risk index				0.323	
Low risk	89 (89.0)	93 (93.0)	182 (91.0)		1
High risk	11 (11.0)	7 (7.0)	18 (9.0)		1.64 (0.61–4.42)
mSCORE risk index				<0.001	
Low risk	64 (64.0)	93 (93.0)	157 (78.5)		1
High risk	36 (36.0)	7 (7.0)	43 (21.5)		7.47 (3.13–17.84)

RA, rheumatoid arthritis; SCORE, Systematic Coronary Risk Evaluation; mSCORE, modified Systematic Coronary Risk Evaluation.

By analyzing the presence of hypertension in the study subjects, the results showed similar rates of this comorbidity in both groups. In a meta-analysis by Boyer et al.,[12] with 15 case–control studies selected with 2956 cases and 2713 controls from 1950 to 2008, no difference was observed in the presence of hypertension in both groups. Although there are inherent factors which contribute to the increase of blood pressure, for example, a lower endothelium-derived nitric oxide expression, higher endothelin and angiotensin II production, and use of certain medications (*e.g.*, leflunomide, nonsteroidal anti-inflammatory drugs and corticosteroids), these factors *per se* are not enough to determine a difference in prevalence of hypertension among RA patients *versus* controls without the disease.

Dyslipidemia was a common finding, but this finding was not more frequent than in the control group. Moreover, Urowitz[13] found slightly higher levels of total cholesterol in patients diagnosed with RA when compared to patients without the disease. One of the features of the lipid profile of these patients was also observed, that is, blood levels of HDL were lower than in the general population. Toms et al.[14] mention that such comorbidity affects 55–65% of RA patients, both in early-stage and late-stage disease. Turning their attention to blood levels of HDL in the groups studied, these authors found lower levels of HDL in RA population. In this same study, the authors mention that, in addition to genetic predisposition (which may be a potential cause of dyslipidemia in these patients), other factors would be acting, such as inflammatory disease activity, physical inactivity due to illness, and use of certain medications.

In comparison with the general population, patients diagnosed with RA are at a twofold increased risk to suffer a cardiovascular event; and the magnitude of this increase is comparable to the risk of cardiovascular events in patients with type 2 diabetes mellitus.[15] Such figures reinforce the importance of identifying RA patients diagnosed with underlying DM, for this knowledge can avoid unfavorable outcomes. In this study, in comparison with RA group, the control group showed a tendency for a twofold increased prevalence of DM, but without statistical significance. Changes in blood glucose levels of RA patients can be explained by modifiable factors such as abdominal obesity, use of antihypertensive agents, disease activity, and the use of corticosteroids.[16] In a meta-analysis by Boyer et al.,[12] the frequency of DM in RA patients was higher than that in the control group ($p = 0.003$); and other studies also found similar findings.[17,18]

Another important comorbidity studied in this manuscript was smoking, with a similar frequency in both case and control groups. In a historical cohort study, Kremers et al.[19] found a prevalence of 52% of smoking in RA patients ($p = 0.004$) and of 43% in the group without the disease. Another meta-analysis, which reinforces the higher frequency of smokers in RA patients *versus* the general population, was conducted by Boyer et al.,[12] with OR = 1.56 (95% CI 1.35–1.80; $p < 0.00001$). It is believed that the low frequency of smoking in RA patients compared with historical cohorts is derived from the more detailed information received by patients about the harmful effects of this habit; patients are aware that this habit would result in lower response to treatment, more severe disease and increased cardiovascular risk.

The tools designed to assess cardiovascular risk in the general population, such as the Framingham score, cannot predict the actual cardiovascular risk in RA patients, because, despite the key role of inflammation in the development of atherosclerosis, in clinical practice this factor is overlooked in many risk stratification tools. Crowson et al.,[20] in a study of 525 RA patients aged less than 30 years, analyzed Framingham and Reynolds scores for assessment of cardiovascular risk. These authors concluded that these scores substantially underestimate cardiovascular risk in RA patients (both genders), mainly in advanced age, in RF-positive subjects, and with persistently high rates of ESR, which is an important marker of inflammatory activity of the disease. Such outcomes can result in missed opportunities for preventive medical interventions, and also create a false sense of security in medical practice in the prediction of the actual cardiovascular risk to which patients are subjected.

The SCORE project was established in 2003 by ESC (European Society of Cardiology) in collaboration with the Third Joint Task Force in order to develop a risk assessment system for clinical practice in Europe. To carry out this project, data from cohort studies from 12 European countries, totaling 205,178 people, were used, representing 2.7 million person-years of follow-up. The 10-year risk of a fatal cardiovascular disease event was calculated, and "age" was used as a measure of risk exposure time, instead of being considered as a risk factor; such calculations were made for high- and low-risk areas for cardiovascular events.

Then, the group developed a simple matrix for risk calculation, providing a direct estimate of 10-year risk of a fatal cardiovascular disease event in a format suitable for the limitations of clinical practice.[21]

In a study by Peters et al.[11] that aimed to develop evidence-based recommendations from the European League Against Rheumatism (EULAR) in RA, ankylosing spondylitis and psoriatic arthritis patients, the orientation of the authors was that in countries in which there was no evaluation guidelines for cardiovascular risk in these populations, the SCORE risk index should be used. In another study conducted by Rosales Alexander et al.,[22] the authors observed a significant association among the SCORE risk index and CRP levels ($p < 0.034$), the presence of extra-articular manifestations ($p < 0.048$), more than 10 years of disease duration ($p < 0.001$), suggesting a relationship of cardiovascular risk and RA severity with cumulative duration of inflammation maintained over the years. These data provided information that allowed the EULAR committee of experts make an adjustment of calculations for the SCORE risk index for patients with at least two out of three of the following factors (a disease with >10 years, RF and/or anti-CCP positivity, and presence of extra-articular manifestations), with the use of a multiplying factor of 1.5 to obtain the modified SCORE risk index (mSCORE).[11]

In our study, it is worthwhile to note that RA patients demonstrated a greater tendency for obtaining a higher prediction of 10-year risk of a fatal cardiovascular disease event when using the classical SCORE matrix, and that the significance of this difference was established with the use of the modified SCORE risk index, with the application of a multiplying factor of 1.5 to the subgroup. This risk difference, found in RA patients, is in accordance with the higher prevalence of cardiovascular events and of mortality from this cause, a fact already confirmed in several epidemiological studies previously conducted.

The study by Gómez-Vaquero et al.,[23] with 200 RA patients, aimed to assess the impact of EULAR recommendations on the cardiovascular risk approach. Its authors found that 11% of patients to whom the classical SCORE risk index was applied and 14% of those assessed with the mSCORE were classified as of high-risk (≥5%) for 10-year risk of a fatal cardiovascular disease event.

Data such as these emphasize the need to incorporate those factors inherent to the disease to cardiovascular risk stratification tools in RA patients; these factors *per se* increase the cardiovascular mortality rates.

We can conclude that, according to the EULAR recommendations, the application of the modified SCORE matrix in RA patients allows us to recognize, in this population at risk, a subgroup of patients with a higher 10-year risk of a fatal cardiovascular disease event in need of an early and intensive pharmacological intervention and of the use of therapeutic targets to determine a lower risk of future cardiovascular events.

Conflicts of interest

The authors declare no conflicts of interests.

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